Orthopedic Treatment for Class II Malocclusion with Functional Appliances and Its Effect on Upper Airways: A Systematic Review with Meta-Analysis

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Review

Orthopedic Treatment for Class II Malocclusion with Functional Appliances and Its Effect on Upper Airways: A Systematic Review with Meta-Analysis

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Keywords: Class II malocclusion; mandibular retrognathism; orthopedic treatment; dentofacial orthopedics; orthodontics; functional appliances; clinical trials; systematic review; meta-analysis

1. Introduction

1.1. Background

Skeletal Class II malocclusion is the most common clinical entity the orthodontist is faced with [1] and is often due to a retrognathic mandible [2]. Among growing patients with a retrognathic mandible, orthopedic advancement of the mandible and its dentition with functional appliances is often performed with considerable success. However, functional appliances are now believed to have mostly dentoalveolar effects [3,4] and more limited effects on skeletal components [5–7].

At the same time, severe mandibular retrognathism has been linked to obstructive sleep apnea (OSA) [8] due to a retrodisplacement of the tongue and hyoid bone that may lead to a concomitant upper airway constriction [9,10]. Inversely, therapeutic advancement of the mandible with functional appliances among OSA patients has been shown to be an effective means to improve clinical OSA parameters [11]. Therefore, it might be reasonable to expect that functional appliance therapy among patients with skeletal Class II malocclusion might be associated with a beneficial effect on the patient's airways [12] and possibly breathing function [13].

A previous systematic review on the subject [14] concluded that early treatment with functional appliances had positive effects on the upper airway, especially on oropharyngeal dimensions, in growing skeletal Class II patients and might decrease potential risk of OSA for growing patients in the future. However, this review only covered literature published only up to the start of 2017, while its conclusions might be influenced by existing methodological issues like lack of an a priori protocol [15], incomplete handling of risk of bias within studies according to the latest Cochrane guidelines [16], issues with the data synthesis (double-counting of controls from multiarm studies, outdated statistical modelling, lack of sensitivity analyses) [17], and no assessment of the quality of meta-evidence [18]. Finally, that systematic review only assessed overall effects, did not associate them with differences between removable/fixed appliances [3,4] and did not assess any patient risk factors.

1.2. Objective

Therefore, the aim of this systematic review was to compare the effects of functional appliance treatment for Class II malocclusion on the upper airway dimensions with natural occurring growth in untreated Class II patients.

2. Materials and Methods

2.1. Protocol, Registration, and Review Question

This review's protocol was made a priori, registered in PROSPERO (CRD42019125897) with all post hoc changes transparently reported (Appendix A). The conduct and reporting of this review are guided by the Cochrane Handbook [19] and the PRISMA statement [20], respectively. The focused question this review tried to answer is: "Does functional appliance therapy of growing Class II patients lead to an increase in the upper airway dimensions to a degree greater than expected by natural growth alone?".

2.2. Eligibility Criteria

Based on the Participants-Intervention-Comparison-Outcome-Study design (PICOS) schema and as few randomized trials exist on this matter, included were randomized and nonrandomized clinical studies on systemically healthy growing human patients of any age (<18 years), sex, and ethnicity with Class II malocclusion with mandibular retrognathism receiving orthopedic functional appliance treatment without any limitations on language, publication year, or status. Excluded were nonclinical studies, animal studies, and case reports/series, as well as studies with obstructive sleep apnea patients, studies without functional appliance treatment, and studies without an untreated longitudinal Class II control group. The primary outcome for this review was the total volume of the upper airways or any specific airway compartment assessed with Cone Beam Computerized Tomography (CBCT). Secondary outcomes included other measures of airway dimensions in terms of linear distances or areas, measured either on lateral cephalograms or CBCTs and in either upright or supine position.

2.3. Information Sources and Search

Eight electronic databases were searched without restrictions from inception to 20 October 2020 (Table S1), while ClinicalTrials.gov Directory of Open Access Journals, Digital Dissertations, metaRegister of Controlled Trials, WHO, Google Scholar, and the reference/citation lists of included articles or existing systematic reviews were manually searched.

2.4. Study Selection

Two authors (D.B. and R.S.) screened the titles and/or abstracts of search hits to exclude obviously inappropriate studies, prior to checking their full texts. Any differences between the two reviewers were resolved by discussion with the last authors (T.E. and S.N.P.).

2.5. Data Collection Process and Items

Data from included studies was collected independently by two authors (D.B. and R.S.) with the same way to resolve discrepancies using predefined/piloted forms covering: (a) study characteristics (design, clinical setting, and country), (b) patient characteristics (age and sex), (c) eligibility criteria for patient selection, (d) treatment details (appliance and duration), and (e) outcome measurement modality.

2.6. Risk of Bias of Individual Studies

The risk of bias of included nonrandomized studies was assessed with a custom tool based on the ROBINS-I ("Risk Of Bias In Nonrandomized Studies—of Interventions") [16]. Assessment of the risk of bias was likewise independently performed by two authors (DB, RS) with the same approach being applied to resolve discrepancies.

2.7. Data Synthesis and Summary Measures

An effort was made to maximize data for the analysis; where data were missing, they were calculated by ourselves. As the outcome of upper airway dimensions is bound to be affected by patient and treatment-related characteristics (baseline dimensions, growth potential, compliance, and response to treatment), a random-effects model was a priori deemed appropriate to calculate the average distribution of true effects, based on clinical and statistical reasoning [21], and a restricted maximum likelihood variance estimator with improved performance was used according to recent guidance [22]. Mean differences (MDs) with their corresponding 95% confidence intervals (CIs) were used, while the standardized mean difference (SMD) was decided post hoc to combine similar measurements of nasopharyngeal volume (Appendix A). The extent and impact of between-study heterogeneity was assessed by inspecting the forest plots and by calculating the tau^2 (absolute heterogeneity) or the I^2 statistics (relative heterogeneity). I^2 defines the proportion of total variability in the result explained by heterogeneity, and not chance, while also considering the heterogeneity's direction (localization on the forest plot) and uncertainty around heterogeneity estimates [23]. The 95% random-effects predictive intervals were calculated to incorporate observed heterogeneity and predict expected results in a future treatment [24].

2.8. Additional Analyses and Risk of Bias across Studies

Possible sources of heterogeneity were a priori planned to be sought through random-effects subgroup analyses and meta-regressions in meta-analyses of at least five trials, according to the following factors: appliance type (removable or fixed), patient age, patient sex, and treatment duration. Reporting biases were assessed with contour-enhanced funnel plots and Egger's test [25] for meta-analyses with ≥10 studies.

The overall quality of meta-evidence (i.e., the strength of clinical recommendations) was rated using the Grades of Recommendations, Assessment, Development and Evaluation (GRADE) approach [18] following recent guidance for nonrandomized studies [26]. The produced forest plots were augmented with contours denoting the magnitude of the observed effects (Appendix A) to assess heterogeneity, clinical relevance, and imprecision [17].

Robustness of the results was checked for meta-analyses ≥ 5 studies with sensitivity analyses based on (i) the inclusion of prospective versus retrospective studies, (ii) unequal duration of treatment/observation between treated/control groups, (iii) inadequate matching (assessed with Cohen's d for baseline measurements of each outcome), and (iv) studies with inadequate versus inadequate samples, with the cut-off set at 25 patients/group. All analyses were run in Stata version 14.0 (StataCorp LP, College Station, TX, USA) by one author (S.N.P.) and the dataset was openly provided [27]. All p values were two sided with α = 5%, except for the test of between-studies or between-subgroups heterogeneity where α-value was set as 10% [28].

3. Results

3.1. Study Selection

A total of 2095 hits were retrieved by the literature database search and another 6 records were identified manually (Figure 1). After removing duplicates and eliminating nonrelevant reports by title/abstracts, 185 full-text papers were checked against the eligibility criteria (Table S2). In the end, 20 publications pertaining to 20 unique studies were included in this review.

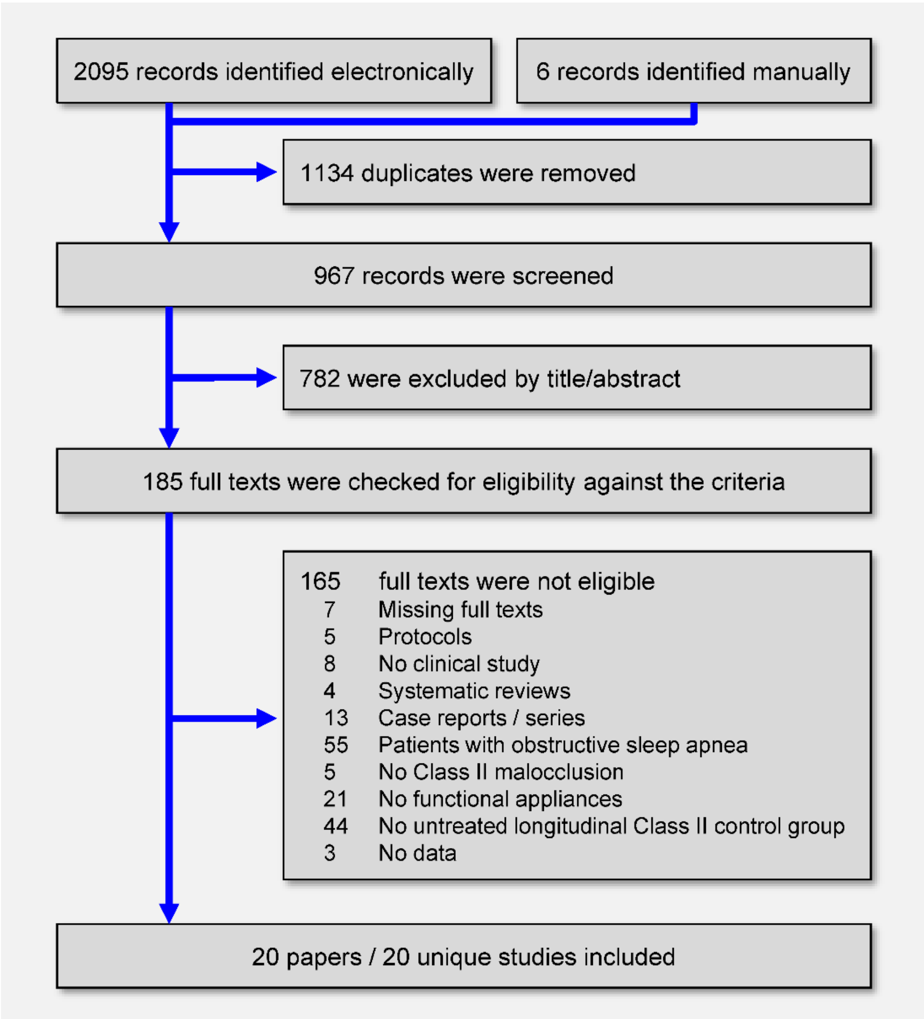

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the identification and selection of studies.

3.2. Study Characteristics

All 20 included studies [29–48] were nonrandomized (Table 1), with only 4 studies (20%) being prospective. All studies were conducted within a university setting (one jointly with a hospital) in 9 different countries (Brazil, Egypt, India, Italy, Pakistan, Spain, Sweden, Turkey, and the United States of America). The included studies were all published as journal papers and were in English, except from one study that was in Turkish.

Table 1. Characteristics of included studies.

Study	Design; Setting; Country *	Patients (M/F); Age †	Appliance (Active Duration)	Radio-Graph
Aksu 2017 [29]	rNRS; Uni; TR	Exp: 16 (4/12); 10.3 Control: 19 (9/10); 10.2	Exp: Activator (15.6) Control—(12.0)	Lateral ceph
Alhammadi 2019 [30]	pNRS; Uni; EG	Exp1: 23 (0/23); 11.9 Exp2: 21 (0/21); 13.5 Control: 18 (0/18); 11.3	Exp1: Twin Block (Tx end) Exp2: Forsus FRD (Tx end) Control—(as Exp1–2)	CBCT
Ali 2015 [31]	rNRS; Uni; PK	Exp: 42 (21/21); 10.4 Control ‡: 32 (16/16); 10.1	Exp: Twin Block +FA (36.4) Control—(36.0)	Lateral ceph
Atik 2017 [32]	rNRS; Uni; TR	Exp1: 15 (4/11); 8.9 Exp2: 15 (6/9); 10.6 Control: 10 (6/4); 9.3	Exp1: Fränkel-2 (14.3) Exp2: X-Bow (8.6) Control—(14.8)	Lateral ceph
Bavbek 2016 [33]	rNRS; Uni; TR	Exp: 18 (10/8); 13.6 Control: 19 (8/11); 12.7	Exp: Forsus FRD (8.7) Control—(11.9)	Lateral ceph
Cortese 2020 [34]	rNRS; Uni; IT	Exp: 10 (7/3); 10.9 Control: 10 (5/5); 10.1	Exp: Activator/Twin Block (21.6) Control—(40.8)	Lateral ceph
Drosen 2018 [35]	rNRS; Uni; SE	Exp: 13 (13/0); 12.4 Control ‡: 13 (13/0); 12.1	Exp: Herbst (21.6) Control—(25.2)	Lateral ceph
Elfeky 2015 [36]	pNRS; Uni; EG	Exp: 18 (0/18); 10.0–12.0 Control: 18 (0/18); 10.0–12.0	Exp: Twin Block (8.0) Control—(8.0)	CBCT
Entrenas 2019 [37]	pNRS; Uni; ES	Exp: 40 (20/20); 9.8 Control: 20 (10/10); 9.1	Exp: Twin Block (Tx end) Control—(12.0–24.0)	Lateral ceph
Fabiani 2017 [38]	rNRS; Uni; IT	Exp: 28 (13/15); 8.4 Control ‡: 21 (14/7); 8.5	Exp: Fränkel-2 (14.6) Control—(16.0)	Lateral ceph
Ghodke 2014 [39]	pNRS; Uni; IN	Exp: 20 (11/9); 8.0–13.0 Control: 18 (9/9); 8.0–14.0	Exp: Twin Block (6.0) Control: ± sectionals (6.0)	Lateral ceph
Goymen 2019 [40]	rNRS; Uni, TR	Exp1: 15 (7/8); 12.1 Exp2: 15 (7/8); 14.5 Control ‡: 10 (NR); 13.0	Exp1: Twin Block (Tx end) Exp2: Forsus FRD (Tx end) Control—(6.0)	Lateral ceph
Jena 2013 [41]	rNRS; Uni; IN	Exp1: 16 (9/7); 12.8 Exp2: 21 (11/10); 11.4 Control 16 (9/7); 10.6	Exp1: MAPA4 (6.2) Exp2: Twin Block (9.4) Control: ± sectionals (9.9)	Lateral ceph
Kilinc 2018 [42]	uNRS; Uni; TR	Exp: 19 (11/8); NR Control: 19 (7/12); NR	Exp: Activator (11.5) Control—(11.3)	Lateral ceph
Oliveira 2020 [43]	rNRS; Uni; BR	Exp: 24 (15/9); NR Control: 18 (10/8); NR	Exp: Herbst (8.0) Control: Pre-Tx (10.4)	CBCT
Ozbek 1998 [44]	rNRS; Uni; TR	Exp: 26 (11/15) 11.5 Control: 15 (7/8) 11.3	Exp: Activator±headgear (17.4) Control—(23.0)	Lateral ceph
Pavoni 2017 [45]	uNRS; Uni; IT	Exp: 51 (27/24); 9.9 Control: 31 (15/16); 10.1	Exp: Activator (21.6) Control—(22.8)	Lateral ceph
Rizk 2016 [46]	rNRS; Uni; US	Exp: 20 (7/13); 11.7 Control: 73 (NR); NR	Exp: MARA+FA (27.4) Control—(NR)	CBCT
Rongo 2020 [47]	rNRS; Hosp/Uni; IT	Exp: 34 (21/13); 11.1 Control: 34 (25/9); 10.4	Exp: Sander (14.8) Control—(13.9)	Lateral ceph
Ulusoy 2014 [48]	rNRS; Uni; TR	Exp: 16 (8/8); 11.4 Control: 19 (8/11); 12.1	Exp: Activator (11.0) Control—(11.4)	Lateral ceph

* given with the country's ISO 3166 alpha-2 code, † given as mean (one value) or if mean not reported, given as range (two values), ‡ historical control from growth study or archive. CBCT, cone beam computerized tomography; ceph, cephalogram; Exp, experimental group; FA, fixed appliance (braces); FRD, fatigue-resistant device; MAPA4, Mandibular Protraction Appliance-IV; MARA, Mandibular Anterior Repositioning Appliance; pNRS, prospective nonrandomized study; Pract, private practice; rNRS, retrospective nonrandomized study; Tx, treatment; Uni, university clinic; uNRS; nonrandomized study with unclear design.

The eligible studies included a total of 969 patients (536 treated/433 untreated), to a median sample size of 40.5 patients/study (range: 20–93 patients/study). Among the 20 studies reporting the patients' gender, 47.9% of the patients were male (424 of the total 886), while from the 16 studies reporting mean age, the average across studies was 10.9 years (range of average age/study 8.4–14.5 years). The identified studies used dental Class II molar relationship, cephalometric skeletal anteroposterior jaw relationship, overjet, or vertical jaw configuration as eligibility criteria to include patients, while 5 studies (25%) also included explicit reporting of no respiratory problems (Table S3). Removable functional appliances (Activator, Fränkel-2, Twin Block, or Sander appliance) were used in 16 studies, while fixed functional appliances (Herbst, Forsus Fatigue Resistant Device, Mandibular Protraction Appliance-IV, Mandibular Anterior Repositioning Appliance, or X-Bow appliance) were used in 8 studies (with 4 studies using both removable and fixed appliances). One study [32] also included a prefabricated myofunctional appliance (Trainer 4 Kids), but this was omitted from the review, due to the different modus operandi [49]. One study [44] incorporated headgear to the Activator for anchorage reinforcement, while another study [31] also included a second phase treatment with braces after a first phase with Twin Block. Airway dimensions were assessed by lateral cephalograms in 16 (80%) of the studies and by CBCT in the remaining 4 (20%)—all of them made in an upright position. All studies reported outcome results before and after treatment with functional appliances, while only one study [35] reported long-term follow-up after treatment (6 years).

3.3. Risk of Bias within Studies

The risk of bias of included nonrandomized studies is summarized in Table 2 and given in detail in Table S4. For most studies, inclusion of patients in the study was not based on any factor that could influence treatment outcome (85%), and the treatment/control groups were clearly defined (95%). Treated/untreated patients were explicitly reported to be selected from the same source and time in only half (50%) of the studies, while the rate of adequate matching at baseline for potential confounders (age, sex, malocclusion, airway dimensions, and treatment/observation duration) between treated/control patients ranged from 35% to 65%. Finally, no study blinded the person measuring the cephalometric/CBCT variables, while the sample size was deemed to be adequate (≥50 patients) in 4 (20%) studies. All included studies were judged to be in critical risk of bias, as issues existed for at least three domains per study.

Table 2. Risk of bias summary of included nonrandomized studies.

Question	Yes/Probably Yes	No/Probably No	No Information
Was the study prospective?	5 (25%)	15 (75%)	–
Was selection of patients based on any factor that could influence the outcome (malocclusion, airways, compliance, missed appointments, breakages)?	3 (15%)	17 (85%)	–
Were FA/CTR groups clearly defined?	19 (95%)	1 (5%)	–
Were FA/CTR patients treated/observed at the same place/time?	10 (50%)	4 (20%)	6 (30%)
Were FA/CTR patients matched for baseline age?	11 (55%)	5 (25%)	4 (20%)
Were FA/CTR patients matched for baseline sex?	13 (65%)	5 (25%)	2 (10%)
Were FA/CTR patients matched for baseline malocclusion?	12 (60%)	5 (25%)	3 (15%)
Were FA/CTR patients matched for baseline airway measurements?	7 (35%)	13 (65%)	–
Was the use of other appliances the same among FA/CTR patients?	14 (70%)	6 (30%)	–
Was the observation period similar for FA/CTR patients?	9 (45%)	7 (35%)	4 (20%)
Were FA/CTR patients measured exactly the same way?	20 (100%)	–	–
Were FA/CTR patients measured blindly?	–	20 (100%)	–
Was the adequate sample? (25 patients per group)	4 (20%)	16 (80%)	–

CTR, untreated control group; FA, functional appliance group.

3.4. Results of Individual Studies and Data Synthesis

The results of studies not included in any meta-analyses are given in Table S5. Functional appliances were associated with a statistically significant but clinically irrelevant reduction in hypopharynx dimensions compared to untreated controls. Additionally, functional appliances were associated with statistically significant increases in nasopharynx dimensions, oropharynx cross-section, and pharynx height—with the increase in nasopharynx being also clinically relevant.

Meta-analyses of the effects of functional appliances on upper airway dimensions are given in Table 3. Orthopedic therapy with functional appliances was associated with statistically significant increases in the volume of both the nasopharynx (3 studies; SMD = 0.95; 95% CI = 0.36 to 1.54; $p = 0.002$) and the oropharynx (4 studies; MD = 2356.14 mm^3; 95% CI = 1276.36 to 3435.92 mm^3; $p < 0.001$; Figure 2) compared to natural growth.

Moderate heterogeneity existed among studies (I^2 60% and 69%, respectively), which, however, influenced only the precise quantification of the improvement seen through treatment (as all included studies were on the same side of the forest plot).

Furthermore, functional appliance therapy was associated with statistically significant increases in (i) the minimal constricted axial area of pharyngeal airway (2 studies; MD = 59.91 mm^2); (ii) superoposterior airway space (8 studies; MD = 1.63 mm); (iii) middle airway space (11 studies; MD = 1.25 mm); (iv) inferior airway space (10 studies; MD = 1.32 mm); (v) McNamara's lower pharynx dimension (3 studies; MD = 2.31 mm); (vi) lower adenoid thickness (2 studies; MD = 1.16 mm); and (vii) pharyngeal dimension at the epiglottal base (4 studies; MD = 0.70 mm). Heterogeneity was relatively moderate, except from the meta-analyses of middle and inferior airway space, where considerable heterogeneity was seen ($I^2 > 75\%$).

3.5. Subgroup and Meta-Regression Analyses

Differences in the effects of removable and fixed functional appliances were assessed in Table 4 and tested formally with subgroup interaction for meta-analyses of at least 5 studies. For most outcomes, removable functional appliances showed considerable greater benefits in terms of airway dimensions than fixed appliances, like nasopharynx volume (SMDs of 1.64 and 0.73, respectively), superoposterior airway space (MDs of 1.41 and 1.08 mm, respectively), middle airway space (MDs of 1.37 and 1.02 mm, respectively), and inferior airway space (MDs of 1.52 and 0.79 mm, respectively). Additionally, increases in McNamara's lower pharynx and sagittal depth of the nasopharynx were seen only with removable functional appliances and had no significant effect with fixed functional appliances. Furthermore, an effect reversal was seen for the minimal constricted axial area of pharyngeal airway, where an increase was seen with removable appliances and a reduction was seen with fixed appliances. However, all these differences were not confirmed by formal subgroup interaction—possibly due to low statistical power. The only exception was for the primary outcome of oropharynx volume, where removable appliances induced a statistically significantly greater increase than fixed appliances (MDs of 2595.56 and 2303.57 mm^3; $p = 0.04$).

Table 3. Random-effects meta-analyses for the effect of any functional appliance versus untreated controls on airways.

Outcome	Studies	MD (95% CI)	*p*	I^2 (95% CI)	tau^2 (95% CI)	95% Prediction
Superoposterior airway space (mm)	8	1.63 (1.03, 2.23)	<0.001	68% (28%, 92%)	0.42 (0.08, 2.15)	−0.13, 3.39
Posterior airway space (mm)	8	0.52 (−0.20, 1.24)	0.15	47% (0%, 87%)	0.44 (0, 3.44)	−1.34, 2.38
Middle airway space (mm)	11	1.25 (0.53, 1.98)	0.001	81% (58%, 93%)	1.09 (0.36, 3.69)	−1.25, 3.76
Inferior airway space (mm)	10	1.32 (0.34, 2.31)	0.009	90% (76%, 97%)	1.97 (0.75, 6.47)	−2.12, 4.76
McNamara's upper pharynx (mm)	3	1.35 (−0.57, 3.27)	0.17	87% (45%, 99%)	2.45 (0.31, 48.50)	−22.12, 24.82
McNamara's lower pharynx (mm)	3	2.31 (0.79, 3.82)	0.003	70% (0%, 99%)	1.18 (0, 41.05)	−14.64, 19.25
Upper adenoid thickness (AD2-H; mm)	2	0.24 (−2.10, 2.58)	0.84	93% (NE)	2.65 (NE)	NE
Lower adenoid thickness (AD1-Ba; mm)	2	1.16 (0.46, 1.86)	0.001	0% (NE)	0 (NE)	NE
Upper airway thickness (PNS-AD2; mm)	5	0.38 (−0.18, 0.94)	0.19	13% (0%, 89%)	0.06 (0, 3.00)	−0.81, 1.57
Nasopharynx height (PNS-BaN; mm)	2	0.13 (−0.77, 1.02)	0.78	51% (NE)	0.21 (NE))	NE
Upper pharyngeal airway passage (Ptm-UPW; mm)	2	−0.37 (−1.73, 0.99)	0.60	0% (NE)	0 (NE)	NE
Base of epiglottis-posterior pharyngeal wall (V-LPW; mm)	4	0.70 (0.11, 1.29)	0.02	14% (0%, 93%)	0.05 (0, 4.46)	−0.93, 2.33
Sagittal depth of bony nasopharynx (Ba-PNS; mm)	2	1.25 (0.06, 2.43)	0.04	21% (NE)	0.18 (NE)	NE
Minimum axial area (mm^2)	2	59.91 (41.46, 78.35)	<0.001	0% (NE)	0 (NE)	NE
Oropharynx sagittal dimension (mm)	2	1.20 (−2.12, 4.52)	0.48	97% (80%, 100%)	5.58 (0.68, 721.82)	NE
Oropharynx area (units)	2 *	556.10 (−279.88, 1392.08)	0.19	0% (NE)	0 (NE)	NE
Nasopharynx volume (mm^3)	3	0.95 † (0.36, 1.54)	0.002	60% (0%, 98%)	0.16 (0, 5.02)	−5.44, 7.34
Oropharynx volume (mm^3)	4	2356.14 (1276.36, 3435.92)	<0.001	69% (0%, 98%)	>100 (0, >100)	−1931.83, 6644.10

CI, confidence interval; MD, mean difference; NE, not estimable, * Study of Ozbek 1998 omitted due to different measurement method, † SMD used instead of MD due to big differences in the control group baseline measurements.

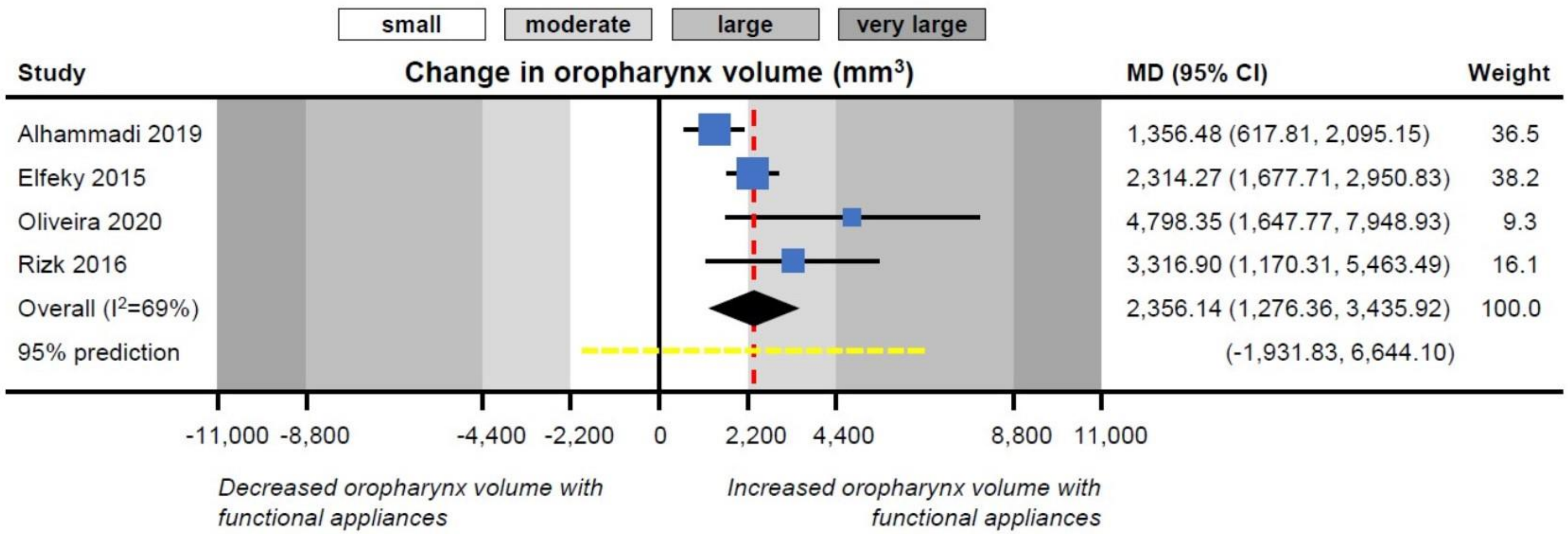

Figure 2. Contour-enhanced forest plot for the effect of functional appliances on oropharynx volume.

Table 4. Subgroup analyses for the effect of removable or fixed functional appliances analyses versus untreated controls on airways.

	All Appliances		Removable Appliances		Fixed Appliances		
Outcome	**MD (95% CI)**	***p***	**MD (95% CI)**	***p***	**MD (95% CI)**	***p***	P_{SG}
Superoposterior airway space (mm)	*n* = 8 1.63 (1.03, 2.23)	<0.001	*n* = 7 1.41 (0.65, 2.17)	<0.001	*n* = 2 1.08 (0.35, 1.82)	0.004	0.20
Posterior airway space (mm)	*n* = 8 0.52 (−0.20, 1.24)	0.15	*n* = 6 0.83 (−0.18, 1.84)	0.11	*n* = 2 0.14 (−0.77, 1.06)	0.76	0.35
Middle airway space (mm)	*n* = 11 1.25 0.53, 1.98)	0.001	*n* = 9 1.37 (0.47, 2.26)	0.003	*n* = 3 1.02 (0.29, 1.75)	0.006	0.26
Inferior airway space (mm)	*n* = 10 1.32 (0.34, 2.31)	0.009	*n* = 8 1.52 (0.32, 2.72)	0.01	*n* = 2 0.79 (0.03, 1.54)	0.04	0.15
McNamara's upper pharynx (mm)	*n* = 3 1.35 (−0.57, 3.27)	0.17	*n* = 2 2.05 (−0.04, 4.14)	0.06	*n* = 1 −0.20 (−1.81, 1.41)	0.81	NT
McNamara's lower pharynx (mm)	*n* = 3 2.31 (0.79, 3.82)	0.003	*n* = 2 2.95 (2.13, 3.78)	<0.001	*n* = 1 0 (−2.67, 2.67)	1.00	NT
Upper adenoid thickness (AD2-H; mm)	*n* = 2 0.24 (−2.10, 2.58)	0.84	*n* = 2 0.24 (−2.10, 2.58)	0.84	–		NT
Lower adenoid thickness (AD1-Ba; mm)	*n* = 2 1.16 (0.46, 1.86)	0.001	*n* = 2 1.16 (0.46, 1.86)	0.001	–		NT
Upper airway thickness (PNS-AD2; mm)	*n* = 5 0.38 (−0.18, 0.94)	0.19	*n* = 4 0.13 (−0.51, 0.78)	0.69	*n* = 1 0.61 (−1.90, 3.12)	0.63	0.73
Nasopharynx height (PNS-BaN; mm)	*n* = 2 0.13 (−0.77, 1.02)	0.78	*n* = 2 0.27 (−1.01, 1.56)	0.68	*n* = 1 0.02 (−0.88, 0.92)	0.97	NT
Upper pharyngeal airway passage (Ptm-UPW; mm)	*n* = 2 −0.37 (−1.73, 0.99)	0.60	n = 2 −0.04 (−1.52, 1.44)	0.96	*n* = 1 −1.12 (−3.06, 0.82)	0.26	NT
Base of epiglottis-posterior pharyngeal wall (V-LPW; mm)	*n* = 4 0.70 (0.11, 1.29)	0.02	*n* = 3 0.65 (−0.33, 1.62)	0.19	*n* = 2 0.51 (−0.46, 1.48)	0.30	NT
Sagittal depth of bony nasopharynx (Ba-PNS; mm)	*n* = 2 1.25 (0.06, 2.43)	0.04	*n* = 2 1.62 (0.57, 2.68)	0.003	*n* = 1 −0.71 (−2.91, 1.49)	0.53	NT
Minimum axial area (mm^2)	*n* = 2 59.91(41.46, 78.35)	<0.001	*n* = 2 91.60 (19.14, 197.56)	0.01	*n* = 1 −26.97 (−44.18, −9.76)	0.002	NT
Oropharynx sagittal dimension (mm)	*n* = 2 1.20 (−2.12, 4.52)	0.48	*n* = 1 −0.65 (−0.89, −0.42)	<0.001	*n* = 2 1.30 (−1.83, 4.42)	0.42	NT
Oropharynx area (units)	*n* = 2 * 556.10 (−279.88, 1392.08)	0.19	*n* = 2 114.35 (98.61, 130.09)	<0.001	*n* = 1 607.00 (−452.17, 1666.17)	0.26	NT
Nasopharynx volume (mm^3)	*n* = 3 0.95 † (0.36, 1.54)	0.002	*n* = 1 1.64 † (0.88, 2.40)	<0.001	*n* = 1 0.73 † (0.10, 1.36)	0.02	NT
Oropharynx volume (mm^3)	*n* = 4 2356.14 (1276.36, 3435.92)	<0.001	*n* = 2 2595.56 (2013.07, 3178.05)	<0.001	*n* = 3 2303.57 (−808.11, 5415.25)	0.15	0.04

CI, confidence interval; MD, mean difference; NT, not tested; P_{SG}, *p* value for subgroup differences. * Study of Ozbek 1998 omitted due to different measurement method, † SMD used instead of MD due to big differences in the control group baseline measurements.

Meta-regression analyses indicated that patient age had a significant influence on the effects of functional appliances (Table 5), as treatment-induced increase in posterior airway space was reduced on average by −0.36 mm (95% CI = −0.75 to 0.03 mm) for each additional year of age. Additionally, a dose-response relationship was seen between increases in airway and treatment duration, as for each additional treatment month, additional increases in superoposterior airway space (coefficient = 0.12 mm; 95% CI = −0.02 to 0.26 mm) and inferior airway space (coefficient = 0.29 mm; 95% CI = 0.12 to 0.45 mm) were seen. Limiting the meta-regressions to only removable functional appliances revealed a greater influence of patient's age on increases in posterior airway space (coefficient = −0.99 mm; 95% CI = −1.91 to −0.08 mm) and of treatment duration on inferior airway space (coefficient = 0.41 mm; 95% CI = 0.26 to 0.56 mm), which might be anticipated, due to the greater treatment effects of removable appliances on the airways.

Table 5. Meta-regression analysis on the effect of functional appliances on airways.

	Any Functional Appliance (Removable/Fixed)			Only Removable Appliances		
Outcome	**Patient Age (Per Year)**	**Male % in Sample (Per %)**	**Treatment Duration (Per Month)**	**Patient Age (Per Year)**	**Male % in Sample (Per %)**	**Treatment Duration (Per Month)**
Upper airway thickness (PNS-AD2; mm)	b = −0.55 p = 0.30	b = −4.03 p = 0.43	b = 0.03 p = 0.26	NT	b = −4.71 p = 0.46	NT
Superoposterior airway space (mm)	b = 0.11 p = 0.69	b = 1.99 p = 0.47	b = 0.12 p = 0.09	b = 0.41 p = 0.41	b = 2.13 p = 0.49	b = 0.17 p = 0.12
Posterior airway space (mm)	b = −0.36 p = 0.06	b = −6.00 p = 0.15	b = 0.07 p = 0.45	b = −0.99 p = 0.04	b = −6.15 p = 0.24	b = 0.07 p = 0.70
Middle airway space (mm)	b = 0.03 p = 0.91	b = −2.59 p = 0.41	b = 0.09 p = 0.28	b = 0.10 p = 0.84	b = −3.40 p = 0.37	b = 0.09 p = 0.48
Inferior airway space (mm)	b = −0.13 p = 0.78	b = 1.56 p = 0.71	b = 0.29 p = 0.003	b = 0.02 p = 0.98	b = 1.61 p = 0.73	b = 0.41 p < 0.001
Base of epiglottis-posterior pharyngeal wall (V-LPW; mm)	b = 0.29 p = 0.46	b = −12.09 p = 0.41	b = −0.13 p = 0.38	NT	b = −13.62 p = 0.55	NT
Oropharynx volume (mm^3)	b = −1256.28 p = 0.17	b = 5027.43 p = 0.23	b = 13.37 p = 0.92	NT	NT	NT

b, meta-regression coefficient; NT, not tested (as less than 5 studies contributed to the analysis).

3.6. Reporting Biases and Sensitivity Analyses

Reporting biases (including the possibility for publication bias) could be assessed only for the meta-analyses of middle and inferior airway space that included at least 10 studies. The funnel plots (Figure S1) indicated asymmetry, which was confirmed by Egger's test in both instances (p = 0.07 and p = 0.006, respectively). However, this was interpreted as small-study effects, with smaller/more imprecise studies reporting greater treatment effects than larger studies.

Sensitivity analyses according to methodological issues of existing studies are seen in Table 6. No significant differences in the meta-analyses were seen between prospective versus retrospective studies nor according to the difference between treatment and observation durations. However, adequate baseline matching had a significant effect on the reported treatment effects of functional appliances. Studies with greater baseline differences between treated/untreated patients (i.e., without adequate matching) reported significantly greater increases in middle (coefficient = 0.93 mm) and posterior airway space (coefficient = 1.86 mm). Furthermore, studies with adequate sample size (≥50 patients) reported significantly higher increases of inferior airway space (coefficient = 2.05 mm) compared to smaller studies. Therefore, future clinical recommendations should be based on studies with adequate baseline matching (preferably through randomization) and with adequate sample size.

Table 6. Sensitivity analyses on the effect of methodological characteristics on the effect of functional appliances on airways.

Outcome	Prospective Vs Retrospective (Ref)	Tx-Ctr Difference in Duration (Per Month)	Tx-Ctr Difference in Baseline Outcome (In Absolute Cohen's d)	Adequate Sample (≥50) vs. Inadequate (Ref)
Upper airway thickness (PNS-AD2; mm)	NE	b = 0.05 p = 0.82	b = 0.38 p = 0.26	b = 0.39 p = 0.59
Superoposterior airway space (mm)	NE	b = −0.07 p = 0.32	b = 0.82 p = 0.15	b = 0.91 p = 0.36
Posterior airway space (mm)	NE	b = 0.04 p = 0.83	b = 1.86 p = 0.08	b = −0.46 p = 0.65
Middle airway space (mm)	b = −0.65 p = 0.62	b = 0.01 p = 0.91	b = 0.93 p = 0.04	b = −1.56 p = 0.27
Inferior airway space (mm)	NE	b = −0.03 p = 0.79	b = 0.51 p = 0.64	b = 2.05 p = 0.09
Base of epiglottis-posterior pharyngeal wall (V-LPW; mm)	b = 0.95 p = 0.26	b = 0.03 p = 0.90	b = −0.48 p = 0.60	b = −1.45 p = 0.29
Oropharynx volume (mm^3)	b = −2334.16 p = 0.27	NE	b = −3586.53 p = 0.36	b = −1406.38 p = 0.51

b, meta-regression coefficient; Ctr, control; NE, not estimable; Ref, reference; Tx, treatment.

3.7. *Quality of Evidence*

The quality of evidence according to GRADE was very low in all instances (downgraded by two points), due to the lack of randomization and the many methodological issues from the identified retrospective studies that might introduce bias. Therefore, our confidence in current estimates is very low and future studies might change current recommendations.

4. Discussion

4.1. *Evidence in Context*

The present systematic review summarizes clinical evidence from existing studies assessing the effects of Class II orthopedic treatment with functional appliances on airway dimensions to untreated Class II controls. A total of 20 studies including 536 treated and 433 untreated Class II patients were finally included in the meta-analyses.

Mandibular advancement with removable or fixed functional appliances was associated with statistically significant increases in airway dimensions directly after treatment compared to what could be expected by Class II growth alone. Specifically, benefits were seen for volume of the naso- and oropharynx, the minimal constricted axial area of pharyngeal airway, and many sagittal measurements of the oropharynx (Table 3). However, many of these changes, especially at the upper pharynx, were small to moderate in magnitude, which means that they might have little clinical relevance. On the contrary, greater effects were seen at the lower part of the pharynx and this indicates that any clinically relevant benefits in airway dimensions or breathing might be attributed in this compartment. There is some evidence indicating that normal patients and patients with sleep-disordered breathing have significant differences in the dimensions of the pharyngeal airway or the thickness of the pharyngeal wall [50], and the lower retropalatal/retroglossal areas are mostly affected [51]. This area has also emerged as a sensitive parameter enabling to consistently assess the patient's respiratory conditions [52]. However, even though increases in airway volume or cross-section might be indicative of improved breathing, functional confirmation through improved nasal airflow resistance, nasal pressure, and patient-relevant outcomes is needed. Some data indicate that treatment with Herbst appliance improved nocturnal breathing in adolescents [53], but the evidence is weak due to the lack of a control group and further studies are needed.

The exact mechanism with which these changes on the upper airway occur is currently unknown, but it might be that the mesial displacement of the lower dentition and the labial flaring of the lower incisors, might cause anterior traction on the tongue and hyoid bone [48], thereby causing adaptive changes of the soft palate and leading to an increase in pharyngeal airway dimensions [33]. This is also compatible with the observation that the soft palate is anteriorly repositioned after functional appliance treatment of Class II [39,41] as the tongue moves away from the palate. However, confirmatory studies are needed.

The effects of orthopedic mandibular advancement on the airways were highly variable among the included studies, which was reflected in between-study heterogeneity. Part of this heterogeneity was explained by several patient- or treatment-related characteristics including patient age, appliance design, and treatment duration (Tables 4 and 5). Removable functional appliances were shown to exert greater changes in the upper airway dimensions than fixed appliances for most of the analyzed variables. This might be due to different skeletal/dentoalveolar effects of removable/fixed appliances that have been previously reported [4]. On the other hand, this might be due to the fact that fixed functional appliances are usually placed on older patients after most deciduous teeth have been shed, whereas removable functional appliances are often placed in the mixed dentition (an age difference also seen among the included studies). This might act as a confounding factor at least to some part, since patient age was consistently associated with the observed airway benefits, both for the whole set of included studies and, specifically, for the subset of removable appliances (Table 5). It is generally believed that, moreover, skeletal effects of functional appliances are more pronounced in patients treated before or during the growth peak [54].

Existing clinical studies only demonstrated the short-term beneficial effect of functional appliances on the upper airways. However, it remains to be seen whether such benefits remain stable in the long term. The sole included study assessing long-term status of treated Class II patients [35] indicated that not only were the benefits of functional appliance treatment retained 6 years afterwards, but a significantly greater post-treatment increase was seen. This is also consistent with previous evidence on the long-term stability of increased airway dimensions among patients with skeletal Class III treated orthopedically with maxillary protraction [55].

4.2. Strengths and Limitations

Among the strengths of the current review can be counted it is a priori registration [15], the extensive searching of the literature, the inclusion of untreated Class II controls, the use of contemporary statistical methods [22], the gauging of the quality of meta-evidence according to GRADE [18], and the transparent open provision of the dataset [56].

On the other hand, some limitations also exist, like the inclusion of weak study designs like retrospective nonrandomized studies [57] with historical controls [58], which might introduce bias. Additionally, most studies had small sample sizes and this can affect the precision of the estimated effects [59]. Moreover, many included studies were inadequately matched in terms of similar baseline airway dimensions, and baseline dissimilarities were associated with inflated treatment effects (Table 6), which is in agreement with previous meta-epidemiological evidence [60,61]. Furthermore, airways before and after treatment were assessed with radiographs done in the upright position and not in a supine position, since most studies were retrospective with nonapneic patients that received functional appliance treatment for their underlying malocclusion and airways were only secondarily assessed. However, changes between supine or upright posture can influence airways measurements [62–64], even though oropharyngeal area measurement from lateral cephalograms can be used as an initial screening measurement to predict the upright upper airway 3D volume [64]. Finally, the small number and the limited reporting of existing studies did not enable extensive subgroup and meta-regression analyses to identify and account for sources of confounding, like patient age, sex, growth pattern, and presence/size of tonsils or adenoid, which might influence the observed results. Further prospective, ideally randomized, studies with open provision of their full dataset [56] will help in shedding on the pure airway effects of orthopedic treatment for Class II malocclusion.

5. Conclusions

Current evidence indicates that orthopedic treatment with functional appliances for Class II malocclusion might be associated with increased volume and dimensions of the upper airways, which are dependent on patient- and treatment-related factors. However, our confidence in these data is very low due to the poor quality of existing studies and their small number. It is crucial that the clinical relevance of such anatomical changes is confirmed by functional analyses of breathing ability before concrete recommendations can be formulated.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/9/12/3806/s1, Figure S1: Contour-enhanced funnel plots for assessing reporting biases and publication bias; Table S1: Literature searches with resulting hits (last search date: 20 October 2020); Table S2: List of studies identified from the literature search and their inclusion/exclusion status, with reasons; Table S3: Malocclusion characteristics of the patients within the included studies; Table S4: Detailed risk of bias of included nonrandomized studies; Table S5: Results of individual studies not included in meta-analyses.

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Appendix A

Additional details of methods and deviations from protocol.
Additional method details:

- When before-and-after treatment values were provided, these were converted to treatment-induced increments (post minus pre) according to Cochrane guidelines assuming a pre/post correlation of 0.75 [19].
- The produced forest plots were augmented with contours denoting the magnitude of expected effects: small (up to half a Standard Deviation [SD]), moderate (half to one SD), large (one to two SDs) and very large (more than 2 SDs). The SD for each outcome's forest plot was based on the average pre-treatment SD of the response variable across all eligible studies for each meta-analysis (rounded up to 2 decimals).

Post hoc changes:

- The standardized mean difference was chosen over the mean difference for the meta-analysis of nasopharynx volume since considerable differences were seen among the measurements of the included studies (one study reporting baseline volume in the control group being twice as large as the volume in the other two studies).

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SUPPLEMENTARY MATERIAL

Orthopedic Treatment for Class II Malocclusion with Functional Appliances and Its Effect on Upper Airways: A Systematic Review with Meta-Analysis

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Table S1. Literature searches with resulting hits (last search date: October 20th, 2020)

Nr	Database	Search strategy	Limits	Hits
1	PubMed	(orthodon* OR orthop* OR "Class II" OR malocclusion OR (mandib* AND retrogn*)) AND ("functional appliance" OR "functional appliances" OR "bite-jumping" OR "mandibular advancement" OR Activator OR Biobloc OR Bionator OR Dynamax OR Eureka OR Forsus OR Frankel OR Fränkel OR Harvold OR Herbst OR "Jasper Jumper" OR Klammt OR "Mandibular Anterior Repositioning Appliance" OR MARA OR MiniScope OR Monobloc OR "Mono-bloc" OR PowerScope OR "R Appliance" OR Sander OR "Schwarz appliance" OR "Schwarz double platte" OR Twinblock OR "Twin-Block" OR "Twin-Blocks" OR Xbow) AND (airway* OR breath* OR "Apnea Hypopnea index" OR "Eppworth Sleepiness Scale")	-	864
2	Embase	Same as PubMed	-	130
3	CDSR	Same as PubMed	-	9
4	CENTRAL	Same as PubMed	-	164
5	DARE	Same as PubMed	-	0
6	Scopus	(TITLE-ABS-KEY ((orthodon* OR orthop* OR "Class II" OR malocclusion OR (mandib* AND retrogn*))) AND TITLE-ABS-KEY (("functional appliance" OR "functional appliances" OR "bite-jumping" OR "mandibular advancement" OR Activator OR Biobloc OR Bionator OR Dynamax OR Eureka OR Forsus OR Frankel OR Fränkel OR Harvold OR Herbst OR "Jasper Jumper" OR Klammt OR "Mandibular Anterior Repositioning Appliance" OR MARA OR MiniScope OR Monobloc OR "Mono-bloc" OR PowerScope OR "R Appliance" OR Sander OR "Schwarz appliance" OR "Schwarz double platte" OR Twinblock OR "Twin-Block" OR "Twin-Blocks" OR Xbow)) AND TITLE-ABS-KEY ((airway* OR breath* OR "Apnea Hypopnea index" OR "Eppworth Sleepiness Scale"))) AND (LIMIT-TO (SUBJAREA , "DENT"))	Dentistry	279
7	Web of Science	Same as PubMed	DENTISTRY ORAL SURGERY MEDICINE	559
8	Virtual Health Library	Same as PubMed	-	90
9	ClinicalTrials.gov	-	-	-
TOTAL				**2095**

CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DARE, Cochrane Database of Abstracts of Reviews of Effects

Table S2. List of studies identified from the literature search and their inclusion / exclusion status, with reasons.

Nr	Paper	Status
1	{ACTRN} A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Study to Assess The Effects of Intravenous BG9928 on Body Weight in Subjects with Acute Decompensated Heart Failure and Renal Insufficiency. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=ACTRN12608000607370. 2008.	Excluded by title
2	{ACTRN} Feasibility and potential benefits of high-intensity interval cycling for knee osteoarthritic patients: a randomised control feasibility trial? http://wwwwhoint/trialsearch/Trial2aspx?TrialID=ACTRN12616000273482. 2016.	Excluded by title
3	{ACTRN} Mouthguard and positional trainer(vibrating collar) in supine sleep apnoea. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=ACTRN12618000207213. 2018.	Excluded by title
4	{CTRI} Comparison of efficacy of 2 different mouthrinses. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=CTRI/2018/01/011237. 2018.	Excluded by title
5	{CTRI} Home based exercises in pulmonary hypertension. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=CTRI/2010/091/001492. 2011.	Excluded by title
6	{DRKS} a randomized controlled trial investigating the efficacy and benefit of the health program "initiative.rücken" in members of a private health insurance with persistent unspecific low back pain. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=DRKS00015463. 2018.	Excluded by title
7	{DRKS} Influence of non-surgical and surgical orthopedic treatment on stress and depression levels, sympathetic and parasympathetic cardiovascular modulation and baroreflex sensitivity in patients with osteoarthritis. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=DRKS00004602. 2012.	Excluded by title
8	{DRKS} The spinal anesthesia with hyperbaric Lokalanästhestikum performed in the lateral position, compared to general anesthesia in outpatient anesthesia, in terms of effectiveness, process times, hemodynamic stability, perioperative complications, and postoperative pain. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=DRKS00004906. 2013.	Excluded by title
9	{Euctr FR} A double-blind, randomized, placebo-controlled, study evaluating the safety and activity of four escalating single doses of AVE0657 in congestive heart failure patients presenting as Cheyne-Stokes Breathing Syndrome. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=EUCTR2007-002172-34-FR. 2007.	Excluded by title
10	{Euctr IT} Breathing disorders in heart failure: high altitude hypoxia as a model to define diagnostic tools, therapeutic strategies and gender related differences. - ND. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=EUCTR2010-019986-27-IT. 2010.	Excluded by title
11	{Irct138810223051N} Comparison of the effect of intratracheal and intravenous lidocaine on bucking, cough, and emergence time at the end of anesthesia. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=IRCT138810223051N1. 2010.	Excluded by title
12	{Irct2013022712123N} Cost-effectiveness analysis of intravenous propofol anesthesia versus inhalational Isoflurane anesthesia in patients undergo open surgery at Shahroud's Imam Hossein hospital. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=IRCT2013022712123N2. 2013.	Excluded by title
13	{Irct2016081729405N} Effects of 8 weeks of combined aerobic and resistive exercise on fat percentage, quality of life and fatigue in patients with pulmonary sarcoidosis. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=IRCT2016081729405N1. 2016.	Excluded by title
14	{ISRCTN} Therapy-efficacy of a new mode of Automatic Servo-Ventilation in patients with complicated breathing patterns during sleep. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=ISRCTN62161274. 2010.	Excluded by title
15	{KCT} Effects of Core Stabilization Exercise and Hip-targeted Muscles Stretching and Strengthening Exercise on Physical Function and Activity in Patients with Non-specific Low Back Pain. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=KCT0004140. 2019.	Excluded by title
16	{NCT} A Pilot Study in Severe Patients With Takayasu Arteritis. https://clinicaltrialsgov/show/NCT04300686. 2020.	Excluded by title
17	{NCT} A Trial to Study the Effects of Pulmonary Rehabilitation Program on Exercise Capacity and Quality of Life in Patients With Severe Form of Chronic Obstructive Pulmonary Disease (COPD). Https://clinicaltrialsgov/show/nct02512549 [Internet]. 2015. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01491264/full.	Excluded by title
18	{NCT} Biofeedback Training, Efficacy Evaluation of Fibromyalgia Treatment, a Pilot Study. https://clinicaltrialsgov/show/NCT04121832. 2019.	Excluded by title
19	{NCT} Effect of Chronic Changes in Heart Rate on Congestive Heart Failure. Https://clinicaltrialsgov/show/nct00389649 [Internet]. 2006. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01513198/full.	Excluded by title
20	{NCT} Effect of Single Rinsing With Three Different Types of Mouthwash on VSC Levels in Morning Breath. https://clinicaltrialsgov/show/NCT04279106. 2020.	Excluded by title
21	{NCT} Effect of the Nursing Process on the Quality of Life of the Patient With Definitive Pacemaker Implantation. https://clinicaltrialsgov/show/NCT03999671. 2019.	Excluded by title
22	{NCT} Effectiveness of Chest Wall Mobilization Program in Improving Respiratory Function for Patients With COPD. https://clinicaltrialsgov/show/NCT04122365. 2019.	Excluded by title
23	{NCT} Effects of Two Different Dry-Needling Techniques for Low Back Pain. https://clinicaltrialsgov/show/NCT03970486. 2019.	Excluded by title
24	{NCT} Efficiency of Methotrexate and Tofacitinib in Mild and Moderate Patients. https://clinicaltrialsgov/show/NCT04299971. 2020.	Excluded by title
25	{NCT} Evaluation of Combined Action Between Natrecor and Furosemide on Kidney and Neurohormone Responses in Chronic Heart Failure: a Phase-IV study704.351 / DSS. Https://clinicaltrialsgov/show/nct00652652 [Internet]. 2008. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01518124/full.	Excluded by title
26	{NCT} Evaluation of the Effect of Different Rapid Maxillary Expansion Appliances on Airway by Acoustic Rhinometry. https://clinicaltrialsgov/show/NCT04529057. 2020.	Excluded by title
27	{NCT} Feasibility & Effect of a Tele-rehabilitation Program in Idiopathic Pulmonary Fibrosis (IPF). Https://clinicaltrialsgov/show/nct03548181 [Internet]. 2018. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01660104/full.	Excluded by title
28	{NCT} Ketorolac for Analgesia followiNG Autologous Breast RecOnstructiOn. Https://clinicaltrialsgov/show/nct03007381 [Internet]. 2017. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01560962/full.	Excluded by title
29	{NCT} Nalbuphine Versus Fentanyl As Additives To Bupivacaine In Spinal Anaesthesia For Internal FixationI Of Tibia. Https://clinicaltrialsgov/show/nct03535792 [Internet]. 2018. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01659816/full.	Excluded by title
30	{NCT} Patient Education and Basic Body Awareness Therapy in Hip Osteoarthritis: a Randomized Controlled Trial. Https://clinicaltrialsgov/show/nct02884531 [Internet]. 2016. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01520517/full.	Excluded by title
31	{NCT} Pelvic Health and Physical Therapy to Improve Lives of Prostate Cancer Patients Undergoing Prostatectomy. https://clinicaltrialsgov/show/NCT04027270. 2019.	Excluded by title
32	{NCT} Polygraphic Evaluation of the Effects of Different Rapid Maxillary Expansion Appliances on Sleep Quality. https://clinicaltrialsgov/show/NCT04529213. 2020.	Excluded by title
33	{NCT} Pulmonary Rehabilitation Program and PROactive Tool. https://clinicaltrialsgov/show/NCT02437994. 2015.	Excluded by title
34	{NCT} SheppHeartCABG - Phase One Rehabilitation After Coronary Artery Bypass Grafting. https://clinicaltrialsgov/show/NCT02290262. 2014.	Excluded by title
35	{NCT} Surgical Adhesive Drapes for Prevention and Healing of Wound Infections After Total Hip Arthroplasty. Https://clinicaltrialsgov/show/nct02707302 [Internet]. 2016. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01556492/full.	Excluded by title
36	{NCT} The Effect of Diaphragmatic Breathing Exercise on Pain, Anxiety, and Depression. https://clinicaltrialsgov/show/NCT04225169. 2020.	Excluded by title
37	{NCT} The Effect of Kinesio Taping on Pulmonary Function and Functional Capacity in Patients With Chronic Heart Failure. Https://clinicaltrialsgov/show/nct03597646 [Internet]. 2018. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01661386/full.	Excluded by title
38	{NCT} The Effect of N-Acetylcystein on Quality of Life and Air Trapping During Rest and After Exercise. https://clinicaltrialsgov/show/NCT00476736. 2007.	Excluded by title

39	{NCT} The Goal of This Study is to Evaluate the Effect of Ultrasound Guided Erector Spinae Plane Block on Postoperative Pain After Major Abdominal Surgeries. https://clinicaltrialsgov/show/NCT04382209. 2020.	Excluded by title
40	{NCT} The Use of Fibrin Sealant to Reduce Post Operative Pain in Cleft Palate Surgery. Https://clinicaltrialsgov/show/nct02953145 [Internet]. 2016. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01559734/full.	Excluded by title
41	{NCT} Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure. https://clinicaltrialsgov/show/NCT00733343. 2008.	Excluded by title
42	Abi-Ramia LBP. Avaliação tridimensional da via aérea superior de pacientes com apneia obstrutiva do sono que utilizaram aparelho de avanço mandibular. 2009:93-.	Excluded by title
43	Achilleos S, Krogstad O, Lyberg T. Surgical mandibular advancement and changes in uvuloglossopharyngeal morphology and head posture: a short- and long-term cephalometric study in males. Eur J Orthod. 2000;22(4):367-81.	Excluded by title
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51	Alcalde LFA. Avaliação das alterações nas vias aéreas superiores através de tomografia computadorizada Cone-Beam em pacientes submetidos à cirurgia ortognática de avanço bimaxilar. 2017:77-.	Excluded by title
52	Amini M, Heravi F, Zandi B, Eslami S, Mohajerzadeh M, Rohani M. The effect of mandibular advancement device on physiologic parameters and volumetric MRI in mild to moderate obstructive sleep apnea-a randomized controlled trial. Sleep Medicine. 2017;40:e14-e5.	Excluded by title
53	Andrade LLd, Rodrigues J. Tratamento da síndrome do respirador bucal com mordida aberta através da aparatologia ortopédica funcional. J bras ortodontia ortop maxilar. 1996;1(2):3-13.	Excluded by title
54	Aoki A, Prahl-Andersen B. Mandibular distraction osteogenesis for treatment of extreme mandibular hypoplasia. Am J Orthod Dentofacial Orthop. 2007;132(6):848-55.	Excluded by title
55	Aragão W. Tratamento da mordida aberta anterior, com disto-relação basal com o regulador de função Aragão V (RFA V). J bras ortodontia ortop maxilar. 1996;1(4):23-31.	Excluded by title
56	Aragão W. Tratamento precoce da classe III com o Regulador de Função Aragão III. J bras ortodon ortop facial. 1998;3(18):16-22.	Excluded by title
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61	Aude Celis M. La terapéutica de ortopedia dentofacial y su efecto en la función pulmonar. Rev Círc Argent Odontol. 1999;28(186):24-31.	Excluded by title
62	Awad M, Gouveia C, Zaghi S, Camacho M, Liu SYC. Changing practice: Trends in skeletal surgery for obstructive sleep apnea. Journal of Cranio-Maxillofacial Surgery. 2019;47(8):1185-9.	Excluded by title
63	Azevedo JCM, Cavalcanti AH, Muxfeldt ES. Blood pressure variation on cardiopulmonary test after continuous positive airway pressure therapy in resistant hypertensive patients with obstructive sleep apnea. Sleep science. 2019;12:27-8.	Excluded by title
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65	Baccetti T, Franchi L, Mucedero M, Cozza P. Treatment and post-treatment effects of facemask therapy on the sagittal pharyngeal dimensions in Class III subjects. Eur J Orthod. 2010;32(3):346-50.	Excluded by title
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68	Bangiyev JN, Traboulsi H, Abdulhamid I, Rozzelle A, Thottam PJ. Sleep architecture in Pierre-Robin sequence: The effect of mandibular distraction osteogenesis. Int J Pediatr Otorhinolaryngol. 2016;89:72-5.	Excluded by title
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70	Brunetto DP, Velasco L, Koerich L, Araujo MT. Prediction of 3-dimensional pharyngeal airway changes after orthognathic surgery: a preliminary study. Am J Orthod Dentofacial Orthop. 2014;146(3):299-309.	Excluded by title
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882	Bellerive A, Montpetit A, El-Khatib H, Carra MC, Remise C, Desplats E, et al. The effect of rapid palatal expansion on sleep bruxism in children. Sleep and breathing. 2015;19(4):1265-71.	Excluded; no functional appliance
883	Chen Y, Zhang J, Rao N, Han Y, Ferraro N, August M. Independent risk factors for long-term skeletal relapse after mandibular advancement with bilateral sagittal split osteotomy. International Journal of Oral and Maxillofacial Surgery. 2020;49(6):779-86.	Excluded; no functional appliance
884	Cheng-Hui Lin C, Wang PF, Ray Han Loh S, Lau HT, Sheng-Ping Hsu S. Maxillomandibular Rotational Advancement: Airway, Aesthetics, and Angle's Considerations. Sleep Med Clin. 2019;14(1):83-9.	Excluded; no functional appliance
885	do Vale F, Rodrigues ML, Francisco I, Roseiro A, Santos I, Caramelo F, et al. Short-term pharyngeal airway space changes after mandibular advancement surgery in Class II patients-a two-dimensional retrospective study. Orthod Craniofac Res. 2019;22(2):81-6.	Excluded; no functional appliance
886	do Vale F, Rodrigues ML, Francisco I, Roseiro A, Santos I, Caramelo F, et al. Short-term pharyngeal airway space changes after mandibular advancement surgery in Class II patients—a two-dimensional retrospective study. Orthodontics and Craniofacial Research. 2019;22(2):81-6.	Excluded; no functional appliance
887	Foltan R, Rybinova K. The impact of mandibular advancement on the upper airway patterns--cephalometric study. Prague Med Rep. 2007;108(2):147-54.	Excluded; no functional appliance
888	Furche S, Edwards SP, Aronovich S, Hummon G, Shah KB, Conley RS. 3D Airway changes using cone beam computed tomography in patients following mandibular advancement surgery with and without constriction. Orthod Craniofac Res. 2019;22 Suppl 1:36-42.	Excluded; no functional appliance
889	Gurani SF, Di Carlo G, Thorn JJ, Ingerslev J, Cattaneo PM, Pinholt EM. Two-Year Postoperative Upper Airway Cone-Beam Computed Tomographic Outcomes Based on a Verified Upper Airway Analysis Following Bimaxillary Orthognathic Surgery. Journal of Oral and Maxillofacial Surgery. 2019;77(7):1435-45.	Excluded; no functional appliance
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891	Kapadia H, Susarla S, Hopper R. Orthodontic considerations in combined orthodontic-surgical management of achondroplasia. Cleft Palate-Craniofacial Journal. 2019;56(1):125.	Excluded; no functional appliance
892	Kiliç B, Amuk NG, Hacioğlu Z, Demirbaş AE. The Effect of Bimaxillary Surgery on the Airway Morphology in Class III Patients: Taking Into Account the Head Posture During Walking. J Craniofac Surg. 2019;30(6):1686-91.	Excluded; no functional appliance
893	Nishanth R, Sinha R, Paul D, Uppada UK, Rama Krishna BV, Tiwari P. Evaluation of Changes in the Pharyngeal Airway Space as a Sequele to Mandibular Advancement Surgery: A Cephalometric Study. Journal of Maxillofacial and Oral Surgery. 2020;19(3):407-13.	Excluded; no functional appliance
894	Niskanen I, Kurimo J, Järnstedt J, Himanen SL, Helminen M, Peltomäki T. Effect of Maxillomandibular Advancement Surgery on Pharyngeal Airway Volume and Polysomnography Data in Obstructive Sleep Apnea Patients. J Oral Maxillofac Surg. 2019;77(8):1695-702.	Excluded; no functional appliance
895	Okuno K, Furuhashi A, Nakamura S, Suzuki H, Arisaka T, Taga H, et al. Japanese Cross-Sectional Multicenter Survey (JAMS) of Oral Appliance Therapy in the Management of Obstructive Sleep Apnea. Int J Environ Res Public Health. 2019;16(18).	Excluded; no functional appliance
896	Rückschloß T, Ristow O, Berger M, Engel M, Freudlsperger C, Hoffmann J, et al. Relations between mandible-only advancement surgery, the extent of the posterior airway space, and the position of the hyoid bone in Class II patients: a three-dimensional analysis. Br J Oral Maxillofac Surg. 2019;57(10):1032-8.	Excluded; no functional appliance
897	Sahoo NK, Agarwal SS, Datana S, Bhandari SK. Effect of Mandibular Advancement Surgery on Tongue Length and Height and Its Correlation with Upper Airway Dimensions. Journal of Maxillofacial and Oral Surgery. 2020;19(4):624-9.	Excluded; no functional appliance
898	Tsui WK, Yang Y, McGrath C, Leung YY. Improvement in quality of life after skeletal advancement surgery in patients with moderate-to-severe obstructive sleep apnoea: a longitudinal study. International Journal of Oral and Maxillofacial Surgery. 2020;49(3):333-41.	Excluded; no functional appliance
899	Tsui WK, Yang Y, McGrath C, Leung YY. Mandibular distraction osteogenesis versus sagittal split ramus osteotomy in managing obstructive sleep apnea: A randomized clinical trial. J Craniomaxillofac Surg. 2019;47(5):750-7.	Excluded; no functional appliance

900	Wiedemeyer V, Berger M, Martini M, Kramer FJ, Heim N. Predictability of pharyngeal airway space dimension changes after orthognathic surgery in class II patients: A mathematical approach. J Craniomaxillofac Surg. 2019;47(10):1504-9.	Excluded; no functional appliance
901	Afzal E, Fida M. Evaluation of the change in the tongue posture and in the hyoid bone position after Twin Block appliance therapy in skeletal class II subjects. Dental and Medical Problems. 2019;56(4):379-84.	Excluded; no control group
902	Ali B, Shaikh A, Fida M. CHANGES IN ORO-PHARYNGEAL AIRWAY DIMENSIONS AFTER TREATMENT WITH FUNCTIONAL APPLIANCE IN CLASS II SKELETAL PATTERN. J Ayub Med Coll Abbottabad. 2015;27(4):759-63.	Excluded; no control group
903	Arora V, Sharma R, Chowdhary S. Comparative evaluation of treatment effects between two fixed functional appliances for correction of Class II malocclusion: A single-center, randomized controlled trial. Angle Orthod. 2018 May;88(3):259-266.	Excluded; no control group
904	Celikoglu M, Buyuk SK, Ekizer A, Unal T. Pharyngeal airway effects of Herbst and skeletal anchored Forsus FRD EZ appliances. Int J Pediatr Otorhinolaryngol. 2016;90:23-8.	Excluded; no control group
905	Ciavarella D, Lo Russo L, Mastrovincenzo M, Padalino S, Montaruli G, Giannatempo G, et al. Cephalometric evaluation of tongue position and airway remodelling in children treated with swallowing occlusal contact intercept appliance (S.O.C.I.A.). Int J Pediatr Otorhinolaryngol. 2014;78(11):1857-60.	Excluded; no control group
906	Dalla Torre D, Burtscher D, Widmann G, Rasse M, Puelacher T, Puelacher W. Long-term influence of mandibular advancement on the volume of the posterior airway in skeletal Class II-patients: a retrospective analysis. Br J Oral Maxillofac Surg. 2017;55(8):780-6.	Excluded; no control group
907	Erbas B, Kocadereli I. Upper airway changes after Xbow appliance therapy evaluated with cone beam computed tomography. Angle Orthod. 2014;84(4):693-700.	Excluded; no control group
908	Fantini SMd, Andrighetto AR. Estudo da correlação entre a alteração do espaço aéreo orofaríngeo e as mudanças da posição natural da cabeça e da altura facial ânter-inferior em indivíduos assintomáticos, com maloclusões de classe II de angle, submetidos à desprogramação neuromuscular com placa oclusal. Ortodontia. 2004;37(2):14-21.	Excluded; no control group
909	Godt A, Koos B, Hagen H, Goz G. Changes in upper airway width associated with Class II treatments (headgear vs activator) and different growth patterns. Angle Orthod. 2011;81(3):440-6.	Excluded; no control group
910	Gómez SPP. Tomografia computadorizada de feixe cônico para avaliação do tratamento da classe II divisão 1ª com o aparelho Herbst no espaço aéreo faríngeo. 2010:95-.	Excluded; no control group
911	Gopal R, Tripathi T, Rai P, Kanase A. Three-dimensional assessment of pharyngeal airway space by MRI in class II division 1 patients treated by twin block appliance. Journal of Clinical and Diagnostic Research. 2018;12(9):ZC20-ZC3.	Excluded; no control group
912	Gu M, Savoldi F, Hägg U, McGrath CPJ, Wong RWK, Yang Y. Upper Airway Changes following Functional Treatment with the Headgear Herbst or Headgear Twin Block Appliance Assessed on Lateral Cephalograms and Magnetic Resonance Imaging. ScientificWorldJournal. 2019;2019:1807257.	Excluded; no control group
913	Gul Amuk N, Kurt G, Baysal A, Turker G. Changes in pharyngeal airway dimensions following incremental and maximum bite advancement during Herbst-rapid palatal expander appliance therapy in late adolescent and young adult patients: a randomized non-controlled prospective clinical study. Eur J Orthod. 2019;41(3):322-30.	Excluded; no control group
914	Hourfar J, Kinzinger GS, Meissner LK, Lisson JA. Effects of two different removable functional appliances on depth of the posterior airway space : A retrospective cephalometric study. J Orofac Orthop. 2017;78(2):166-75.	Excluded; no control group
915	Isidor S, Di Carlo G, Cornelis MA, Isidor F, Cattaneo PM. Three-dimensional evaluation of changes in upper airway volume in growing skeletal Class II patients following mandibular advancement treatment with functional orthopedic appliances. Angle Orthod. 2018;88(5):552-9.	Excluded; no control group
916	Julku J, Pirilä-Parkkinen K, Pirttiniemi P. Airway and hard tissue dimensions in children treated with early and later timed cervical headgear-a randomized controlled trial. European journal of orthodontics. 2018; 40(3):285-95.	Excluded; no control group
917	Kinzinger G, Czapka K, Ludwig B, Glasl B, Gross U, Lisson J. Effects of fixed appliances in correcting Angle Class II on the depth of the posterior airway space: FMA vs. Herbst appliance--a retrospective cephalometric study. J Orofac Orthop. 2011;72(4):301-20.	Excluded; no control group
918	Koay WL, Yang Y, Tse CS, Gu M. Effects of Two-Phase Treatment with the Herbst and Preadjusted Edgewise Appliances on the Upper Airway Dimensions. ScientificWorldJournal. 2016;2016:4697467.	Excluded; no control group
919	Lin YC, Lin HC, Tsai HH. Changes in the Pharyngeal Airway and Position of the Hyoid Bone After Treatment With a Modified Bionator in Growing Patients With Retrognathia. Journal of Experimental and Clinical Medicine. 2011;3(2):93-8.	Excluded; no control group
920	Manni A, Pasini M, Giuca MR, Morganti R, Cozzani M. A retrospective cephalometric study on pharyngeal airway space changes after rapid palatal expansion and Herbst appliance with or without skeletal anchorage. Prog Orthod. 2016;17(1):29.	Excluded; no control group
921	Ozdemir F, Ulkur F, Nalbantgil D. Effects of fixed functional therapy on tongue and hyoid positions and posterior airway. Angle Orthod. 2014;84(2):260-4.	Excluded; no control group
922	Peterson ST. A CBCT Study of Pharyngeal Airway Changes Due to Fixed Functional Appliances. MSc Thesis, Loma Linda University, 2016.	Excluded; no control group
923	Rădescu OD, Colosi HA, Albu S. Effects of rapid palatal expansion (RPE) and twin block mandibular advancement device (MAD) on pharyngeal structures in Class II pediatric patients from Cluj-Napoca, Romania. Cranio. 2020;38(1):22-9.	Excluded; no control group
924	Ravera S, Rollet D, Cugliari G, Deregibus A, Castroflorio T. Interceptive treatment effects of EF preformed appliance in pre-pubertal and pubertal skeletal Class II growing patients: A retrospective controlled study. European Journal of Paediatric Dentistry. 2020;21(2):123-8.	Excluded; no control group
925	Restrepo C, Santamaria A, Pelaez S, Tapias A. Oropharyngeal airway dimensions after treatment with functional appliances in class II retrognathic children. J Oral Rehabil. 2011;38(8):588-94.	Excluded; no control group
926	Schutz TC, Dominguez GC, Hallinan MP, Cunha TC, Tufik S. Class II correction improves nocturnal breathing in adolescents. Angle Orthod. 2011;81(2):222-8.	Excluded; no control group
927	Shetty K, Saidath K, Shetty A, Ravi MS, Shashidhar K, Anushree A. Assessment and comparison of oropharyngeal airway dimensions in skeletal Class II cases treated with forsus FRD and Twin Block Appliances. Nitte University Journal of Health Science. 2017;7(2):8-18.	Excluded; no control group
928	Singh GD, Garcia-Motta AV, Hang WM. Evaluation of the posterior airway space following Biobloc therapy: geometric morphometrics. Cranio. 2007;25(2):84-9.	Excluded; no control group
929	Smailiene D, Intiene A, Dobradziejute I, Kusleika G. Effect of Treatment with Twin-Block Appliances on Body Posture in Class II Malocclusion Subjects: A Prospective Clinical Study. Med Sci Monit. 2017;23:343-52.	Excluded; no control group
930	Temani P, Jain P, Rathee P, Temani R. Volumetric changes in pharyngeal airway in Class II division 1 patients treated with Forsus-fixed functional appliance: A three-dimensional cone-beam computed tomography study. Contemp Clin Dent. 2016;7(1):31-5.	Excluded; no control group
931	Thakur VK, Londhe SM, Kumar P, Sharma M, Jain A, Pradhan I. Evaluation and quantification of airway changes in Class II division 1 patients undergoing myofunctional therapy using twin block appliance. Medical Journal Armed Forces India. 2020.	Excluded; no control group
932	Thereza-Bussolaro C, Oh HS, Lagravère M, Flores-Mir C. Pharyngeal dimensional changes in class II malocclusion treatment when using Forsus® or intermaxillary elastics - An exploratory study. Int Orthod. 2019;17(4):667-77.	Excluded; no control group
933	Verma G, Tandon P, Nagar A, Singh GP, Singh A. Cephalometric evaluation of hyoid bone position and pharyngeal spaces following treatment with Twin block appliance. J Orthod Sci. 2012;1(3):77-82.	Excluded; no control group
934	Vinoth SK, Thomas AV, Nethravathy R. Cephalomteric changes in airway dimensions with twin block therapy in growing Class II patients. J Pharm Bioallied Sci. 2013;5(Suppl 1):S25-9.	Excluded; no control group
935	Yassaei S, Tabatabaei Z, Ghafurifard R. Stability of pharyngeal airway dimensions: tongue and hyoid changes after treatment with a functional appliance. Int J Orthod Milwaukee. 2012;23(1):9-15.	Excluded; no control group
936	Zhang C, He H, Ngan P. Effects of twin block appliance on obstructive sleep apnea in children: a preliminary study. Sleep Breath. 2013;17(4):1309-14.	Excluded; no control group
937	Abdalla Y, Brown L, Sonnesen L. Effects of a fixed functional appliance on upper airway volume: A 3-dimensional cone-beam computed tomography study. Am J Orthod Dentofacial Orthop. 2020;158(1):40-9.	Excluded; control group not Class II
938	Han S, Choi YJ, Chung CJ, Kim JY, Kim KH. Long-term pharyngeal airway changes after bionator treatment in adolescents with skeletal Class II malocclusions. Korean J Orthod. 2014;44(1):13-9.	Excluded; control group not Class II

939	Iwasaki T, Sato H, Suga H, Minami A, Yamamoto Y, Takemoto Y, et al. Herbst appliance effects on pharyngeal airway ventilation evaluated using computational fluid dynamics. Angle Orthod. 2017;87(3):397-403.	Excluded; control group not Class II
940	Iwasaki T, Takemoto Y, Inada E, Sato H, Saitoh I, Kakuno E, et al. Three-dimensional cone-beam computed tomography analysis of enlargement of the pharyngeal airway by the Herbst appliance. Am J Orthod Dentofacial Orthop. 2014;146(6):776-85.	Excluded; control group not Class II
941	Li L, Liu H, Cheng H, Han Y, Wang C, Chen Y, et al. CBCT evaluation of the upper airway morphological changes in growing patients of class II division 1 malocclusion with mandibular retrusion using twin block appliance: a comparative research. PLoS One. 2014;9(4):e94378.	Excluded; control group cross-sectional
942	Li L, Wu W, Yan G, Liu L, Liu H, Li G, et al. Analogue simulation of pharyngeal airflow response to Twin Block treatment in growing patients with Class II(1) and mandibular retrognathia. Sci Rep. 2016;6:26012.	Excluded; control group cross-sectional
943	Aras I, Pasaoglu A, Olmez S, Unal I, Aras A. Upper airway changes following single-step or stepwise advancement using the Functional Mandibular Advancer. J Orofac Orthop. 2016;77(6):454-62.	Excluded; control group receiving treatment
944	Hanggi MP, Teuscher UM, Roos M, Peltomaki TA. Long-term changes in pharyngeal airway dimensions following activator-headgear and fixed appliance treatment. Eur J Orthod. 2008;30(6):598-605.	Excluded; control group receiving treatment
945	E HW. Pharyngeal airway increases with LARS treatment for retrognathia. Cranio. 2020;38(1):30-3.	Excluded; inadequate data
946	Gu M, Lin Y, McGrath CPJ, Hagg U, Wong RWK, Yang Y. Evaluation of the upper airway dimensions following Herbst appliance treatment in adolescents: A retrospective study. Apos Trends in Orthodontics. 2020;10(3):153-63.	Excluded; inadequate data
947	H Williamson E. Pharyngeal airway increases with LARS treatment for retrognathia. Cranio. 2018 May 31:1-4.	Excluded; inadequate data
948	Aksu M, Gorucu-Coskuner H, Taner T. Assessment of upper airway size after orthopedic treatment for maxillary protrusion or mandibular retrusion. Am J Orthod Dentofacial Orthop. 2017;152(3):364-70.	Included
949	Alhammadi MS, Elfeky HY, Fayed MS, Ishaq RAR, Halboub E, Al-Mashraqi AA. Three-dimensional skeletal and pharyngeal airway changes following therapy with functional appliances in growing skeletal Class II malocclusion patients : A controlled clinical trial. J Orofac Orthop. 2019 Sep;80(5):254-265.	Included
950	Ali B, Shaikh A, Fida M. Effect of Clark's twin-block appliance (CTB) and non-extraction fixed mechano-therapy on the pharyngeal dimensions of growing children. Dental Press J Orthod. 2015;20(6):82-8.	Included
951	Atik E, Gorucu-Coskuner H, Kocadereli I. Dentoskeletal and airway effects of the X-Bow appliance versus removable functional appliances (Frankel-2 and Trainer) in prepubertal Class II division 1 malocclusion patients. Australian Orthodontic Journal. 2017;33(1):3-13.	Included
952	Bavbek NC, Tuncer BB, Turkoz C, Ulusoy C, Tuncer C. Changes in airway dimensions and hyoid bone position following class II correction with forsus fatigue resistant device. Clin Oral Investig. 2016;20(7):1747-55.	Included
953	Cortese M, Pigato G, Casiraghi G, Ferrari M, Bianco E, Maddalone M. Evaluation of the Oropharyngeal Airway Space in Class II Malocclusion Treated with Mandibular Activator: A Retrospective Study. J Contemp Dent Pract. 2020;21(6):666-72.	Included
954	Drosen C, Bock NC, von Bremen J, Pancherz H, Ruf S. Long-term effects of Class II Herbst treatment on the pharyngeal airway width. Eur J Orthod. 2018;40(1):82-9.	Included
955	Elfeky HY, Fayed MMS. Three-dimensional effects of twin block therapy on pharyngeal airway parameters in Class II malocclusion patients. Journal of the World Federation of Orthodontists. 2015;4(3):114-9.	Included
956	Entrenas I, González-Chamorro E, Álvarez-Abad C, Muriel J, Menéndez-Díaz I, Cobo T. Evaluation of changes in the upper airway after Twin Block treatment in patients with Class II malocclusion. Clin Exp Dent Res. 2019;5:259–268.	Included
957	Fabiani G, Galvan Galvan J, Raucci G, Elyasi M, Pacheco-Pereira C, Flores-Mir C, et al. Pharyngeal airway changes in pre-pubertal children with Class II malocclusion after Frankel-2 treatment. Eur J Paediatr Dent. 2017;18(4):291-5.	Included
958	Ghodke S, Utreja AK, Singh SP, Jena AK. Effects of twin-block appliance on the anatomy of pharyngeal airway passage (PAP) in class II malocclusion subjects. Prog Orthod. 2014;15:68.	Included
959	Göymen M, Mourad D, Güleç A. Evaluation of Airway Measurements in Class II Patients Following Functional Treatment. Turk J Orthod. 2019 Mar;32(1):6-10.	Included
960	Jena AK, Singh SP, Utreja AK. Effectiveness of twin-block and Mandibular Protraction Appliance-IV in the improvement of pharyngeal airway passage dimensions in Class II malocclusion subjects with a retrognathic mandible. Angle Orthod. 2013;83(4):728-34.	Included
961	Kilinc DD, Sayar G. Pharyngeal airway changes of patients after Class II activator treatment. Selcuk Dent J 2018;5:8-12.	Included
962	Oliveira PM, Cheib-Vilefort PL, de Pársia Gontijo H, Melgaço CA, Franchi L, McNamara JA, Jr., et al. Three-dimensional changes of the upper airway in patients with Class II malocclusion treated with the Herbst appliance: A cone-beam computed tomography study. Am J Orthod Dentofacial Orthop. 2020;157(2):205-11.	Included
963	Ozbek MM, Memikoglu TU, Gogen H, Lowe AA, Baspinar E. Oropharyngeal airway dimensions and functional-orthopedic treatment in skeletal Class II cases. Angle Orthod. 1998;68(4):327-36.	Included
964	Pavoni C, Cretella Lombardo E, Franchi L, Lione R, Cozza P. Treatment and post-treatment effects of functional therapy on the sagittal pharyngeal dimensions in Class II subjects. Int J Pediatr Otorhinolaryngol. 2017;101:47-50.	Included
965	Rizk S, Kulbersh VP, Al-Qawasmi R. Changes in the oropharyngeal airway of Class II patients treated with the mandibular anterior repositioning appliance. Angle Orthod. 2016;86(6):955-61.	Included
966	Rongo R, Martina S, Bucci R, Festa P, Galeotti A, Alessandri Bonetti G, et al. Short-term effects of the Sander bite-jumping appliance on the pharyngeal airways in subjects with skeletal Class II malocclusion: A retrospective case-control study. Journal of Oral Rehabilitation. 2020.	Included
967	Ulusoy C, Canigur Bavbek N, Tuncer BB, Tuncer C, Turkoz C, Gencturk Z. Evaluation of airway dimensions and changes in hyoid bone position following class II functional therapy with activator. Acta Odontol Scand. 2014;72(8):917-25.	Included

Table S3. Malocclusion characteristics of the patients within the included studies.

Study	Malocclusion
Aksu 2017 [29]	ANB>5º; Class II molar relationship; no respiratory problems
Alhammadi 2019 [30]	Overjet≥5mm; ≥½ Class II molar relationship
Ali 2015 [31]	ANB>4º; SNB<78º; SN-ML 28-36º; bilateral Class II molar relationship
Atik 2017 [32]	Class II molar relationship; Class II/1; SNB<78º; overjet≥4mm
Bavbek 2016 [33]	ANB>4º; Class II/1; SNB<80º; overjet>5mm; SN-ML 26-38º; no respiratory problems
Cortese 2020 [34]	ANB>4º; overjet >4mm; Class II/1; retrognathic mandible
Drosen 2018 [35]	ANB>4º; Class II molar relationship (for the EG)
Elfeky 2015 [36]	ANB>4º; overjet>4mm; Class II molar relationship; no respiratory problems
Entrenas 2019 [37]	Mandibular Class II
Fabiani 2017 [38]	Class II/1; overjet>4mm; ANB>4º; SNB<78º; bilateral Cl. ½-full II molar relationship; cervical vertebrae maturation stage 1-2; good compliance (for the experimental group)
Ghodke 2014 [39]	Bilateral Class II molar relationship; SNA 79-84º; SNB≤º76; overjet=6-10mm; FMA 20-28º
Goymen 2019 [40]	Class II/1; ANB>4º; overjet>5mm
Jena 2013 [41]	Class II/1; bilateral Class II molar relationship; overjet=6-10mm; FMA 20-25º; no proclined anterior teeth
Kilinc 2018 [42]	Class II molar relationship; retrognathic mandible; during growth spurt
Oliveira 2020 [43]	Class II; ANB>4º; retrognathic mandible; cervical vertebrae maturation stage 2-5
Ozbek 1998 [44]	Class II molar relationship, ANB>4º; retrognathic mandible; overjet>5mm; no respiratory problems; hand-wrist radiograph $<MP3_{cap}$
Pavoni 2017 [45]	½ or full Class II molar relationship; ANB≥4º; overjet>5mm; normo-/hypo-divergent; cervical vertebrae maturation stage 2-3; sleep disordered breathing (for the experimental group)
Rizk 2016 [46]	Class II molar relationship; ANB≥4.5º; SNB ≤77º; SN-ML≥27º; cervical vertebrae maturation stage<5; no respiratory problems
Rongo 2020 [47]	Full Class II molar relationship; overjet>6mm; retrognathic mandible; cervical vertebrae maturation stage 2-3; SN-ML 26-38º
Ulusoy 2014 [48]	ANB>5º; SNB<80º; overjet>5mm; SN-ML 26-38º; no respiratory problems

Table S4. Detailed risk of bias of included non-randomized studies.

Reference	Aksu 2017	Alhammadi 2019	Ali 2015	Atik 2017	Bavbek 2016	Cortese 2020	Drosen 2018	Elfeky 2015	Entrenas 2019	Fabiani 2017	Ghodke 2014
Was the study prospective?	N	Y	N	N	N	N	N	Y	Y	N	Y
Was selection of patients based on any factor that could influence the outcome (malocclusion, airways, compliance, missed appointments, breakages)?	PN	N	PY	N	N	N	PN	N	PN	PY	PN
Were FA/CTR groups clearly defined?	PY	Y	Y	PY	Y	Y	PN	Y	PY	Y	Y
Were FA/CTR patients treated/observed at the same place/time?	Y	Y	N	NI	PY	NI	N	Y	PY	PY	PY
Were FA/CTR patients matched for baseline age?	Y	PN	Y	N	PN	Y	Y	PY	PY	PY	NI
Were FA/CTR patients matched for baseline sex?	PN	Y	Y	PY	PY	Y	Y	Y	Y	PN	PY
Were FA/CTR patients matched for baseline malocclusion?	PY	PY	PN	Y	PY	Y	Y	PY	NI	PN	PY
Were FA/CTR patients matched for baseline airway measurements?	PY	N	N	N	PY	PY	Y	PY	N	N	PY
Was the use of other appliances the same among FA/CTR patients?	NA	NA	N	NA	PY	NA	PN	NA	NA	NA	PN
Was the observation period similar for FA/CTR patients?	PY	NI	Y	N	N	N	PN	Y	NI	PY	Y
Were FA/CTR patients measured exactly the same way?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were FA/CTR patients measured blindly?	N	N	N	N	N	N	N	N	N	N	N
Was the adequate sample? (25 patients per group)	N	N	Y	N	N	N	N	N	Y	N	N

CTR, untreated control group; FA, fixed appliance group; N, no; NA, not applicable; NI, no information; PN, probably no; PY, probably yes; Y, yes.

Table S4. Detailed risk of bias of included non-randomized studies (*continued*).

Reference	Goymen 2019	Jena 2013	Kilinc 2018	Oliveira 2020	Ozbek 1998	Pavoni 2017	Rizk 2016	Rongo 2020	Ulusoy 2014
Was the study prospective?	N	N	N	N	N	Y	N	N	N
Was selection of patients based on any factor that could influence duration (malocclusion, airways, compliance, missed appointments, breakages)?	N	N	PN	PN	N	PY	PN	PN	PN
Were FA/CTR groups clearly defined?	Y	Y	PY	Y	PY	PY	PY	PY	PY
Were FA/CTR patients treated/observed at the same place/time?	PY	PY	NI	PY	PN	NI	NI	PN	NI
Were FA/CTR patients matched for baseline age?	N	N	NI	NI	PY	PY	NI	PY	PY
Were FA/CTR patients matched for baseline sex?	NI	PN	PN	PY	PY	PY	NI	PY	PN
Were FA/CTR patients matched for baseline malocclusion?	N	PN	N	NI	PY	PY	NI	PY	PY
Were FA/CTR patients matched for baseline airway measurements?	N	PN	N	PN	PN	PN	PN	PN	PY
Was the use of other appliances the same among FA/CTR patients?	NA	PN	NA	N	PN	NA	NA	NA	NA
Was the observation period similar for FA/CTR patients?	NI	PN	Y	PN	N	PY	NI	PY	PY
Were FA/CTR patients measured exactly the same way?	Y	Y	Y	Y	Y	PY	PY	Y	PY
Were FA/CTR patients measured blindly?	N	N	N	N	N	N	N	N	N
Was the adequate sample? (25 patients per group)	N	N	N	N	N	Y	N	Y	N

CTR, untreated control group; FA, fixed appliance group; N, no; NA, not applicable; NI, no information; PN, probably no; PY, probably yes; Y, yes.

Table S5. Results of individual studies not included in meta-analyses.

Study	Appliance	Outcome*	MD (95% CI)	P	CR
Aksu 2017	Activator	Epiglottic airway space (mm)	0.90 (-0.65, 2.45)	0.26	-
Fabiani 2017	Fränkel-2	PNS-H (mm)	0.15 (-0.88, 1.18)	0.78	-
Fabiani 2017	Fränkel-2	Ptm-Ba (mm)	-0.34 (-1.27, 0.59)	0.47	-
Goymen 2019	Twin-Block / FFRD	Hypopharynx dimension (mm)	-0.61 (-0.86, -0.37)	<0.001	No
Goymen 2019	Twin-Block / FFRD	Nasopharynx dimension (mm)	0.66 (0.35, 0.97)	<0.001	Yes
Oliveira 2020	Herbst	Nasal cavity volume (mm^3)	-1513.75 (-4033.94, 1006.44)	0.24	-
Pavoni 2017	Activator	Phw1-Psp (mm)	4.50 (3.88, 5.13)	<0.001	Yes
Pavoni 2017	Activator	lin_U-PNS (mm)	1.60 (1.01, 2.19)	<0.001	No
Rizk 2016	MARA	Oropharynx cross-section (mm)	3.99 (1.98, 6.00)	<0.001	No
Rongo 2020	Sander	Pharynx dimension (on the B-Go line; mm)	0.60 (-1.84, 3.04)	0.63	-
Ulusoy 2014	Activator	Nasopharynx area (mm^2)	160.00 (-371.76, 691.76)	0.56	-
Ulusoy 2014	Activator	Pharynx dimension (at the velum; mm)	0.25 (-1.57, 2.07)	0.79	-

* from explanation of each landmark, consult the original studies.

CI, confidence interval; CR, clinically relevant (judged as effect being larger than one standard deviation of the control group pre-treatment); FFRD, Forsus Fatigue Resistant Device; MARA, Mandibular Anterior Repositioning Appliance; MD, mean difference.

Figure S1. Contour-enhanced funnel plots for assessing reporting biases and publication bias.